



Overlap Syndrome in Respiratory Medicine: Asthma and Chronic Obstructive Pulmonary Disease

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ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent chronic diseases in the general population. Both are characterized by similar mechanisms: airway inflammation, airway obstruction, and airway hyperresponsiveness. However, the distinction between the two obstructive diseases is not always clear. Multiple epidemiological studies demonstrate that in elderly people with obstructive airway disease, as many as half or more may have overlapping diagnoses of asthma and COPD. A COPD-Asthma overlap syndrome is defined as an airflow obstruction that is not completely reversible, accompanied by symptoms and signs of increased obstruction reversibility. For the clinical identification of overlap syndrome COPD-Asthma Spanish guidelines proposed six diagnostic criteria. The major criteria include very positive bronchodilator test [increase in forced expiratory volume in one second (FEV1) $\geq 15\%$ and ≥ 400 ml], eosinophilia in sputum, and personal history of asthma. The minor criteria include high total IgE, personal history of atopy and positive bronchodilator test (increase in FEV1 $\geq 12\%$ and ≥ 200 ml) on two or more occasions. The overlap syndrome COPD-Asthma is associated with enhanced response to inhaled corticosteroids due to the predominance of eosinophilic bronchial inflammation.

The future clinical studies and multicenter clinical trials should lead to the investigation of disease mechanisms and simultaneous development of the novel treatment.

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Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are the most frequent chronic respiratory diseases that affect the general population (1). Traditionally, asthma and COPD are considered to be distinct nosological entities with different pathophysiological mechanisms, clinical manifestations and treat-

ment. COPD is typically caused by tobacco smoking, develops in mid to later life and is characterized by incompletely reversible airflow limitation that results in a progressive decline in lung function leading to premature death. In contrast, asthma is widely recognized as an allergic disease that develops in childhood, characterized physiologically by reversible airflow obstruction, and has an episodic course

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with a generally favorable prognosis, responding well to anti-inflammatory treatment.

However, there is a big number of patients that manifest a significant overlap between these two conditions, which leads to diagnostic and therapeutic doubts (2). A COPD-Asthma overlap syndrome is present to the subjects that prove characteristics from asthma and COPD symptoms at the same time (3).

Definitions

In the last version of Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) 2013 report (4), the scientific committee suggested the following definition of COPD: a common preventable and treatable disease, is characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

The Global Initiative for Asthma (GINA) gives the following definition of asthma (5): "A chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment".

A COPD-Asthma overlap syndrome is defined as an airflow obstruction that is not completely reversible, accompanied by symptoms and signs of increased obstruction reversibility (6). The prevalence of this mixed phenotype is unknown but it is considered that it's percentage increase with age. Soriano et al estimated that approximately 23% COPD patients of ages 50-59 years could have a mixed phenotype (7).

COPD, Asthma and Overlap Syndrome: differences and similarities

COPD and Asthma have three common pathophysiological components of obstructive airway diseases (8): airway inflammation, airway obstruction, and airway hyperresponsiveness.

The airway inflammation is the main component in both conditions. However, the predominant activity of CD4 and eosinophils is proved in asthma, and COPD is driven mostly by the action of neutrophils and CD8.

In overlap syndrome there is no classic type of inflammation. In this way, patients may present asthma with neutrophils (smokers) that

lead the inflammation and confer resistance to steroids (9), and COPD patients that develop an allergic compound determined by hyperactivity of the eosinophils and cytokines they provide, this COPD is well maintained by steroids (10).

The chronic inflammation can transform into an active form triggered by different, exogenous or endogenous factors, usually by respiratory infections. Exacerbations are episodes of worsening symptoms of variable severity. Frequent exacerbations manifest both - asthma and COPD patients with a compromised territory, as comorbidities or poor immune system or an inadequate treatment (11). The frequency of exacerbation determines the increased mortality and the faster decline of the lung function and health status. The main aim of the management of obstructive lung diseases is to prevent the exacerbations and keep the health status with an adequate pathophysiological treatment. That is why it is very important to understand and to assess the inflammatory process in overlap syndrome (12).

The airway obstruction is the component that develops the clinics of these two diseases.

The obstruction in asthma is a reactive one, determined by the response of bronchial muscles (bronchospasm) and the bronchial interstitial edema (13). The great amount of IgE explains this mechanism. When the allergen contacts with IgE the mast cell releases histamine and other proinflammatory mediators, which in contact with different types of receptors make the smooth muscles contract and the vessels to dilate. The dilated vessels become hyperpermeable and lead to the interstitial edema. In asthma the obstruction is reversible, spontaneously or by medical treatment.

In COPD the obstruction is determined by the mucus plugging, the bronchial interstitial edema and the bronchial remodeling (14). The chronic inflammation develops a hyperplasia of the mucus producing cells and the fibroblasts, the hyperplasia and the hypertrophy of the smooth muscles. Thus, the hyperproduction of the mucus, whose evacuation is mostly impossible because of the endured wall and the deteriorated ciliary epithelium, plugs the distal airways.

In overlap syndrome the obstruction may be caused as well by the mucus plugging and by the bronchospasm.

The airway hyperresponsiveness is an exaggerated bronchoconstrictor response to a big variety of stimuli and it is characteristic for the asthma and to the two thirds of patients with COPD (15). At a pathophysiological level, patients with overlap syndrome have evidence of incompletely reversible airflow obstruction (COPD) that can be detected by a reduced

postbronchodilator forced expiratory volume in one second (FEV₁). Also, they have an increased variability of airflow, which can be determined by the increased bronchodilator responsiveness or the bronchial hyperresponsiveness (6).

How to diagnose the COPD-Asthma overlap syndrome?

Majority of specialists in respiratory medicine recognize that asthma and COPD can appear more similar than dissimilar clinically (16).

It is necessary to mention that the overlap syndrome is considered to be one of the four COPD clinical phenotypes, according to the Spanish Guideline for Treatment of stable COPD [17] (Gula Espanola de la EPOC - GesEPOC): non-exacerbator, with emphysema or chronic bronchitis; mixed COPD-asthma; exacerbator with emphysema and exacerbator with chronic bronchitis.

For the clinical identification of this mixed phenotype - overlap syndrome COPD-Asthma Spanish guidelines proposed six diagnostic criteria, which were agreed and grouped in major and minor criteria (2, 17). To establish the diagnosis of overlap syndrome it is necessary that the patient manifests at least one major and two minor criteria, or two major criteria.

The Major Criteria for the identification of the mixed phenotype are:

1. Very positive bronchodilator test (increase of FEV₁ \geq 15% and \geq 400 ml over baseline)
2. Eosinophilia in sputum ($>$ 3%)
3. Personal history of asthma (history before the age of 14')

The Minor Criteria for the identification of the mixed phenotype are:

1. High total IgE
2. Personal history of atopy
3. Positive bronchodilator test (increase in FEV₁ \geq 12% and \geq 200ml over the baseline) on two or more occasions.

Hence, we can conclude that young asthmatics who smoke and develop not fully reversible airflow obstruction can be included into the mixed phenotype category (18).

Treatment of the COPD-Asthma overlap syndrome

The combination of different symptoms of these two different nosological entities results not only in difficulties of diagnosis, but also in difficulties of treatment.

Smoking cessation, oxygen supplementation, pulmonary rehabilitation, vaccines and management of comorbidities are all well

argued interventions. Unfortunately at the moment, there are no randomized clinical trial data to help guide therapeutic interventions in COPD-Asthma overlap syndrome (19). In fact, patients with overlapping asthma and COPD are frequently excluded from treatment trials for either condition (6).

Patients with overlap syndrome, "asthmatic smokers", present a greater degree of bronchial eosinophilic inflammation (20, 21). That is why they have a very good response to inhaled corticosteroids, even if the use of inhaled corticosteroids is not recommended in COPD with FEV₁ $>$ 60%. Therefore, patients with overlap syndrome should be prescribed the inhaled corticosteroids together with long-acting bronchodilators irrespective of the severity of the airflow obstruction, as considered earlier (12). In severe cases a long-acting anticholinergic agents can be added as well. (12, 16).

Conclusion

The overlap syndrome is a disease which has not been studied enough yet. Meanwhile, it should be considered as a nosological entity because of the special clinical manifestations and the high prevalence, especially in elderly patients. The COPD-Asthma overlap syndrome should be treated considering its special pathophysiology. Consequently, the chronic obstructive diseases could be better managed and the quality of life through these patients could be considerably increased. The further clinical studies and multicenter clinical trials should lead to the investigation of disease mechanisms and simultaneous development of the novel treatment.

Conflict of Interest

The authors declare no conflict of interest.

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